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EXAMINER	
WESSENDORF, TERESA D	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 11/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/928,367	DUFFY, DAVID	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,7,27 and 33-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-7, 27 and 33-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 6-7, 27 and 33-35 are pending and under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 6-7, 27 and 33-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons stated in the last Office action and reiterated below.

New Matter

Claims 6, 7, 27 and 33-35 the phrase "wherein detecting modification ***comprises the additional step of quantifying the amount of the inactive MEK or inactive MAPK proteins***..." is not supported in the as-filed specification.

Response to Arguments

Applicant states that support for this amendment can be found in Example 3 (including paragraphs [0135]-[0136] and

Figure 3.) Example 3 discloses inactive MEK/MAPK and the kind of modification made to them (phosphorylation).

In reply, the ***specific modification "phosphorylation"*** recited in Example 3 is not a support for the broad claimed modification. Furthermore, [0135] does not disclose an inhibitor. It discloses only an antibody against the different phosphorylated MAPK, MEK and MEKK.

Written Description

The specification fails to provide an adequate written description of how an inactive MEK and MAPK immobilized on a polymer gel mask has been modified simply by exposing it to a solution of active Raf proteins and MEK and potential inhibitors of RAF or active MEK. It is not apparent from the claims what is being actually claimed i.e., modification of an inactive immobilized MAPK or MEK or the different potential inhibitors of the active Raf or MEK. Example 3 at page 29 describes a method of determining the potential inhibitors by making reference to Figure 3. However, it is not apparent as to the different potential inhibitors of MEK or Raf as the disclosure simply describes broadly inhibitors and not a single specific inhibitor. Furthermore, it does not describe the kind, type, location and other modifications made to the immobilized inactive MEK or MAPK. Does the modification(s) result in the

activation of the inactive MEK or MAPK, if so would the potential inhibitors have no effect on the now activated MEK and MAPK? What would be the differentiating features of the active or inactive MEK such that the inhibitor binds to one and not the other?

Response to Arguments

Applicant states that paragraph [0106] discloses an exemplary pathway that involves proteins A, B and C. Paragraph [0124] discloses that the invention could be used to study biological pathways such as the MAPK cascades. Paragraph [0135] discloses an array that can be used to monitor the Raf/MEK/MEK/MAPK pathway. Applicant further states that the method can be used to study potential inhibitors of the active Raf or MEK.

In response, the claims do not recite for an identification or study of potential inhibitors of the active Raf or MEK. The claims are drawn to detecting modification of the inactive MEK proteins. A patent is not a hunting license it is not a reward for the search (e.g., exploratory study), but compensation for its successful conclusion.

Applicant states that paragraphs [0135]-[0136] and Fig. 3 drawing describes the mechanism of identifying the inhibitor of active Raf.

In response, paragraph [0135] describes antibodies and its binding to phosphorylated members of a signal transduction pathway arrayed onto a surface. There is no inhibitor description in said paragraph [0135]. Neither does paragraph [0136] describe an inhibitor. It describes an enzyme-substrate phosphorylation monitored by a phosphoro-specific antibody. Figure 3 is confusing as to its correspondence to the claims. It is not clear whether the drug candidate is the inhibitor or the role of fluorescent antibody absent recitation of a drug candidate and fluorescent antibody in the claims.

Applicant states that some potential inhibitors are well-known in the art and the method claims screening large variety of potential inhibitors to identify inhibitors of active Raf or MEK.

In response, the as-filed specification does not recite the argued potential inhibitors that are well-known in the art and used specifically for the recited method. As stated above, the claims and arguments are confusing and contradictory. The claims recite a method in detecting modification. Applicant arguments are drawn to identifying potential inhibitors.

Claim Rejections - 35 USC § 112, second paragraph

Claims 6-7, 27 and 33-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to

particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons as repeated below.

A. Claim 35 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the step by which the modification of the inactive MEK proteins or MAPK (not MAP, as claimed) is detected. It is unclear as to the kind, extent and other modifications obtained by the claimed process on the inactive MAPK or MEK immobilized on a substrate. If the immobilized MEK and MAPK are inactive, does its reaction with the active Raf and MEK caused modification of the inactively immobilized MEK and MAPK? The claim is confusing and inconsistent with the description in the disclosure at e.g., page 61, Example 3. The example relates to determining the inhibitors of Raf or MEK. The claim and Example 3 of the disclosure contain the same process steps, yet determine different effect(s).

Response to Arguments

Applicant states that step (e) of the claims recite "detecting modification".

In response, simply reciting the term "detecting" without reciting the step as to the modification that occurred such that detection can be made is insufficient and indefinite.

Applicant states that claim 35 is not limited to any single kind of modification or detection method. Example 3 does disclose one example of the modification i.e., phosphorylation. Paragraph [0135] describes that antibodies that are specific to phosphorylated resides(sic) of MEK and MAPK are incubated on the array.

In response, the single modification recited in Example 3 does not correlate to the claimed process step. Thus, it is unclear as to whether phosphorylation is the kind of modification done in the claim. The claims do not relate to antibody specificity to MEK and MAPK.

Applicant states that Example 3 is not inconsistent with the claims. The method used inhibitors of RAF or MEK that can be identified.

In response, applicant fails to point out how the inhibitors in the claims are identified or the method step in the claims drawn to identifying potential inhibitors.

B. The rejection under this paragraph is withdrawn in view of applicant's statement.

Claim Rejections - 35 USC § 103

Claims 6-7, 27 and 33-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Duesbery (USP 6,485,925) for reasons of record and repeated below. [This rejection is based on the claimed interpretation of detecting inhibitors of the Raf/MEK/MAPK pathway.]

Duesbery discloses assays to identify modulators of LF MAPKK protease activity and LF mimetics of this activity. Duesberry further discloses techniques described in Freshney (1994) can be used. Briefly, the level of invasion of host cells can be measured by using filters coated with Matrigel or some other extracellular matrix constituent. Penetration into the gel, or through to the distal side of the filter, is rated as invasiveness, and rated histologically by number of cells and distance moved. Duesbery further discloses that LF modulators can also be identified using in vitro assays. Such assays are conveniently used for high throughput screening of modulators. For the in vitro assays, recombinant or naturally occurring LF, PA, and MAPKK can be used. For example, recombinant LF can be used in combination with a cell extract that has an activated MAPK pathway, e.g., a Ras/Raf transformed NIH3T3 cell lysate. In

such assays, direct cleavage of MAPKK can be detected, or phosphorylation of MAPKK substrates can be examined. Alternatively, recombinant or naturally occurring MAPKK and LF are incubated together under standard reaction conditions, for direct detection of MAPKK cleavage. In another assay, recombinant or naturally occurring MAPKK and LF or an LF homologue are incubated with an MAPKK substrate such as MBP and/or MAPK, and phosphorylation of the substrate is examined. Duesbery discloses in vitro assays can also be performed without cell extracts, by direct incubation of LF and MAPKK, or by incubation of LF and MAPKK with an MAPKK substrate. LF modulators are optionally added to such assays. After LF and MAPKK are incubated together under suitable reaction conditions (see, e.g., Example IV), MAPKK cleavage is detected by using ELISA. Phosphorylation of an MAPKK substrate can also be used as an assay for LF activity and MAPKK cleavage. For example, LF or an LF mimetic, MAPKK, MAPK, and myelin basic protein (MBP) are incubated together in a kinase buffer, optionally with an LF modulator (see, e.g., Example III). Phosphorylation of either MAPK or MBP can be detected by western blot or ELISA with specific antibodies to phosphorylated MAPK or MBP protein. Any of the assays for compounds that modulate or mimic LF MAPKK protease activity are amenable for use in high throughput screening. High

throughput assays for the activity of a particular product, e.g., LF are well known to those of skill in the art. In addition, high throughput screening systems are commercially available. These systems typically automate entire procedures including all sample and reagent pipetting, liquid dispensing, timed incubations, and final readings of the microplate in detector(s) appropriate for the assay. These configurable systems provide high throughput and rapid start up as well as a high degree of flexibility and customization. The manufacturers of such systems provide detailed protocols the various high throughputs. Such high throughput assays often incorporate solid substrates such as a microtiter dish (e.g., PVC, polypropylene, or polystyrene), polymer bead or other substrate such as paper. Often in the assays of the invention, a molecule such as MAPKK is labeled with a detectable moiety. The effects of LF were tested upon tumor-derived NIH3T3 (490) cells expressing an effector domain mutant form of the human V12HaRas oncogene (V12-S35 Hras). This oncogenic mutant of Ras retains constitutive activation of the Raf-MAPKK-MAPK pathway. Cells transformed with this Ras mutant are tumorigenic, and derived tumors display high levels of MAPK(ERK 1/2) activity. See col. 4, line 7; col. 11, line 50 up to col., 16, line 45; col. 17, line 5 up to col. 18, line 5; col. 20, lines 10- 15; and the different Examples, particularly Example III for the

specifics of the in vitro assay method. Duesbery does not specifically disclose an immobilization of inactive MEK and MAPK on a substrate of the polymer gel contact mask. However, said immobilization would have been obvious to one having ordinary skill in the art at the time the invention was made. The suggested teaching of Duesbery as to the use of microtiter dish of the specific polymer PVC or a filter coated gel, for example, use in high-throughput screening would have led one having ordinary skill in the art to the polymer gel contact mask. One would have reasonable expectation of success since this polymer gel contact mask (or filter) has been successfully employed in the art at the time of the invention.

Response to Arguments

Applicant points out that step (a) of claim 35 recites placing a polymer gel contact mask having holes on a substrate. Step (b) recites immobilizing inactive MEK proteins and inactive MAPK protein on areas on the substrate underlying the holes of the polymer gel contact mask. Furthermore, Duesbery uses the matrigel to culture cells, not to mask a substrate onto which inactive MEK and MAPk proteins can bind.

In response, whether the step is to place a polymer gel contact mask, as argued as opposed to a matrigel on the substrate, as taught by Duesbery is immaterial. The same effect

of identifying inhibitors (or modification as by phosphorylation, as argued above) is achieved. The specification discloses the use in the alternative of a solid support with or without a gasket. Contrary to applicant's arguments Duesbery clearly uses the gel (Matrigel) to coat filters to measure invasion of host cells. Duesbery states:

> Briefly, the level of invasion of host cells can be measured by using ***filters coated with Matrigel*** or some other extracellular matrix constituent. Penetration into the gel, or through to the distal side of the filter, is rated as invasiveness, and rated histologically by number of cells and distance moved. (Emphasis added.)

Thus, applicant's argument is unclear as to "Duesbery uses the matrigel to culture cells." Furthermore, the specification does not disclose a "polymer contact gel mask." Applicant has not shown the essentiality or advantages of the contact mask as opposed to Duesberry's direct or covering the entire substrate with the same polymer gel (matrigel). The claims do not recite that the inactive MEK binds to a polymer gel contact mask. The claims recite only the immobilization of the inactive MEK.

Applicant states that the limitation of claim 34 such as exposing inactive MEK and MAPK proteins to a solution of active RAF and MEK proteins, ATP and potential inhibitors and allowing binding to the active RAF and MEK proteins to the inactive MEK and MAPK proteins are not taught by Duesbery.

In reply, Duesbery would have suggested the step of exposing of inactive MAPPK. Duesbery, as recited above discloses "for example, recombinant LF can be used in combination with a cell extract that has an activated MAPK pathway, e.g., a Ras/Raf transformed NIH3T3 cell lysate. In such assays, direct cleavage of MAPKK can be detected, or phosphorylation of MAPKK substrates can be examined." This presupposes that the MAPK pathway is inactive and is activated when transformed by Raf (step d, as claimed).

Claims 6-7, 27 and 33-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ruggieri et al in view of Mitsuhashi et al (WO 01/07164), as reiterated below. [Based on the detection on the modification of the pathway.]

Ruggieri et al discloses at col.3, lines 10-40 a method in which SRK (a class of proteins involved in cell signal transduction pathways such as MAPK pathways) activates inactive MAPKK polypeptides, i.e., an MAPKK stimulatory activity. This activity can be direct, e.g., by directly acting upon the MAPKK (e.g., phosphorylating it), or it can be indirect where activation is accomplished by acting upon one or more intermediates which then stimulate MAPKK activity. An MAPKK stimulatory activity means, e.g., that SRK, and polypeptides thereof, activate or stimulate a MAPKK protein kinase activity.

MAPKK stimulatory activity can be measured in vivo or in vitro as illustrated in the examples. MAPKK proteins stimulated or activated by SRK include, e.g., MEK. In one type of assay, SRK is co-expressed in a cell with an MAPKK; the MAPKK is isolated, and then assayed for kinase activity using an appropriate substrate, e.g., ERK when MEK is used. The amount of stimulatory activity can be determined by measuring the MAPKK kinase activity from cells transfected with and without SRK. MAPKK stimulatory activity can also be measured in cell-based assays. For instance, cell viability in cell lines defective in MAPKKK activity, such as cell lines lacking Raf, are rescued when transformed with SRK. SRK is a member of a cell signal transduction pathway, one activity of which is to activate gene transcription. Expression analysis can be performed conventionally. For example, high-density oligonucleotide chip arrays can be designed to monitor expression. Such chips can contain all or subsets of the human genome.

Ruggieri at col. 14, line 10 up to col. 15, line 55, discloses a method of regulating a biological response in which SRK, or a homolog thereof, participates, e.g., by being a participant in the biochemical pathway which leads to the ultimate cellular response. For instance, an aspect of the invention relates to methods of modulating signal transduction

in which SRK is involved. Since such signal transduction can lead to various biological responses, including transcriptional activation of certain genes. Thus, the invention relates to methods of controlling expression of these genes by modulating SRK activity. Any of the methods described in, e.g., U.S. Pat. Nos. 5,767,075; 5,753,446; 5,728,536; 5,667,314; and 5,459,036 can be utilized e.g., using SRK. Signal transduction mediated by SRK can be modulated by administering various agents, including a dominant negative SRK gene (see, examples). The method relates to detecting a protein kinase activity in a SRK polypeptide, or a biologically-active polypeptide fragment thereof. Typically, a method of detecting kinase activity in a SRK polypeptide comprises, reacting a human SRK polypeptide, or a biologically-active polypeptide fragment thereof, and a substrate under conditions effective said SRK polypeptide to phosphorylate said substrate; and detecting said phosphorylation of said substrate. Effective conditions include, e.g., appropriate substrates, ATP, co-factors, etc. For SRK kinase assays, substrates can be, e.g., MAPKKs, such as MEK. Kinase activity means, e.g., the ability of SRK to transfer a phosphate group from a phosphate donor (e.g., ATP) to a phosphate acceptor (e.g., MBP). Ruggieri et al also discloses methods of identifying substrates for SRK kinase activity. SRK can be contacted with a test substrate, either in

vivo or in vitro, under conditions effective for phosphorylation to occur. After a suitable time, the substrate can be isolated and probed for the presence of a phosphate residue. As mentioned, a preferable method of detecting phosphorylation is to use radioactive ATP. See, examples for further guidance. The method further relates to identifying agents which modulate a MAPKK stimulatory activity of a human SRK polypeptide, or a biologically-active polypeptide fragment thereof, comprising, administering a test agent to a cell expressing (1) a human SRK polypeptide, or a biologically-active polypeptide fragment thereof, and (2) an MAPKK polypeptide, under conditions effective for said SRK polypeptide to stimulate protein kinase activity of said MAPKK polypeptide; detecting said protein kinase activity; and identifying whether the test agent modulates said stimulatory activity of said SRK polypeptide by comparing the amount of kinase activity in the presence and absence of the test agent. MAPKK stimulatory means, e.g., the ability of SRK to activate the kinase activity of MAPKK, itself. Such stimulation can be direct or indirect, e.g., where SRK stimulates a factor which, in turn, stimulates MAPKK. The stimulatory effect is relatively specific for the MAP kinase cascade. The term "administering" as used, means, e.g., any suitable delivery technique which is adequate to place the agent

in a location where it can elicit an effect. For example, administering can mean contacting a cell or host in an effective manner with the agent of interest, whereby the agent can modulate the activity of interest. See further cols. 25 and 26, Example 1 and 2, respectively. Ruggieri does not teach immobilizing the kinase to a substrate with a polymer gel contact mask (gasket) in a multiwell plate. However, Mitsuhashi et al discloses at page 2, lines 3-5; page 3, lines 21-23 and page 5, lines 28-35 a gasket adapted for use with a multiwell microplate. The use of gasket solves the problem of cross-contaminant, which may occur between adjacent nozzles on the underside of a filter plate.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to use an array with a gasket in the method of Ruggieri. The use of array is conventional in the art and is employed for high throughput screening of compounds. Furthermore, the advantage taught by Mitsuhashi et al in using a gasket(polymer gel mask) in an array or multiwell plates would provide the motivation to one having ordinary skill in the art.

Response to Arguments

Applicant states that Mitsuhashi is not a polymer gel mask as claimed. It is made of hard material, as indicated by the

list at page 1, lines 27-33. The references do not teach immobilizing inactive MEK and MAPK protein on a substrate, as claimed.

In response, applicant's argument that the gasket of Mitsuhashi is made of hard material is not commensurate in scope with the claims. The claim does not preclude the kind of material the gasket is made of. Mitsuhashi recites polymers such as nylon. Furthermore, the specification does not recite that the mask is a gel. Attention is drawn to Ruggieri's Example, e.g., Example 5 which recites for an inactive SRK.

One cannot show non-obviousness by attacking the references individually where the rejection is based on a combination of references. In re Young, 159 USPQ 725 (CCPA 1968). The test for obviousness under 35 USC 103 is not the express suggestion of the claimed invention in any or all of the references but what the references taken collectively would suggest; and inferences which one skilled it in the art would reasonably be expected to draw from the disclosure in the references. In re Preda, 159 USPQ 342 and In re Conrad, 169 UASPQ 170.

Thus, the combined teachings of the prior art render the claimed prima facie obvious at the time of the invention.

No claim is allowed.

Conclusion

1. Sedivy et al disclose kinase inhibitors and methods of use in screening assays and modulators.

2. Palombella et al discloses MEKKI molecules.

It is noted that applicant did not address these two cited references.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571) 272-0812. The examiner can normally be reached on Flexitime. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner
Art Unit 1639

Tdw
October 27, 2006